IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Valerie Legrand et al.

Application No.: 10/826,690 Confirmation No.: 9585

Filed: April 19, 2004 Art Unit: 1618

For: MICROPARTICULATE ORAL GALENICAL FORM FOR THE DELAYED AND CONTROLLED RELEASE OF PHARMACEUTICAL ACTIVE PRINCIPLES

Examiner: L. Schlientz

DECLARATION OF CATHERINE CASTAN

1. My name is Catherine CASTAN.
2. I have been an employee of Flamel Technologies, S.A. since 1992.
3. My position at Flamel Technologies, S.A. is Director of Galenic Department.
4. I have a Ph.D. in Polymer Chemistry.
5. I have worked in the area of pharmaceutical compositions for 21 years.
6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for delayed and controlled release of active principles.
7. I reviewed the office action that issued on September 15, 2009, for U.S. Application No. 10/826,690.
8. I also reviewed EP 1101490 ("Ishibashi"), a reference cited by the Examiner in a 35 U.S.C. § 112, first paragraph, rejection.
9. I believe the Examiner is alleging that Ishibashi has formulations that meet all of the characteristics of Applicant's formulations but do not have the claimed functional dissolution properties. *See,* Office Action at pages 5-6.
10. As one of skill in the art, I believe Ishibashi does not teach the claimed composition. Specifically, Ishibashi does not teach the very small size range of about 200 to about 800 microns.

11. The structure of the coated granules described in Ishibashi is depicted in figure 1 below. A thick layer containing the drug substance is deposited onto an inert carrier of diameter R0 ("nonpareil"). This granule is covered by a coating that controls the release of the drug.

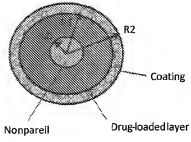

FIGURE 1

12. Below I calculated the **lower limit** of the Ishibashi coated granules particle size, and show that the lower limit of Ishibashi are greater than the particle diameters claimed in this application.

13. The calculations are based on elementary geometric considerations justified by the spherical shape of the inert carrier (*see* Ishibashi, page 9, [0060]), and from the data disclosed in the examples of Ishibashi.

14. Ishibashi, however, does not disclose all of the information necessary to calculate the particle size of the coated granules. It does not disclose the size of the Nonpareil 103 and it does not disclose the concentration of the sucrose solution that was used.

15. Concerning the Nonpareil 103 particle size, the Handbook of Pharmaceutical Excipients, Pharmaceutical Press, second edition (1994) and third edition (2000) (see Appendix) states that at the time of patent application Ishibashi the following particle sizes were available:

> "Particle size distribution: sugar spheres are of a uniform diameter.
> The following sizes are commercially available (US standard sieves):
> 35-40 mesh (450-500μm)
> 30-35 mesh (500-590μm)
> 25-30 mesh (590-710μm)
> 20-25 mesh (710-840μm)
> 18-20 mesh (840-1000μm)
> 16-20 mesh (840-1190μm)
> 14-18 mesh (1000-1410μm)"

Therefore, to calculate the smallest size of coated granules that Ishibashi could have manufactured, I considered that he used the smallest available nonpareil 103, i.e. 35-40 mesh (425-500 μm).

16. To calculate the smallest size of coated granules according to Ishibashi, first set the following variables:

a. M_0 is the mass (in kg) of the neutral beads with specific weight ρ_0 (in kg/m^3)

b. R_0 is the radius of the inert carrier (in m)

c. M_1 is the mass of active plus additives deposited onto the inert layer and ρ_1 the specific mass (in kg/m^3) of this drug loaded layer

d. R_1 is the radius of the drug containing granule (in m)

e. M_2 is the mass of coating with a specific weight ρ_2 (kg/m^3). M_2 is deduced from the mass fraction $M_2/(M_0+M_1)$ given by Ishibashi, and

f. R_2 is the radius of the coated granule (in m).

17. The number of beads is given by:

$$N = \frac{3M_0}{4\pi R_0^3 \rho_0} \qquad (1)$$

18. The mass of drug per particle, m_1, and the mass of coating per particle, m_2, are given by:

$$m_1 = \frac{M_1}{N} \quad \text{and} \quad m_2 = \frac{M_2}{N} \qquad (2)$$

19. From elementary geometry:

$$m_1 = \frac{4\pi}{3}\rho_1\left[R_1^3 - R_0^3\right] \quad \text{and} \quad m_2 = \frac{4\pi}{3}\rho_2\left[R_2^3 - R_1^3\right] \qquad (3)$$

20. Finally the radius R_2 of the particle is given by:

$$R_2 = \left[R_0^3 + \frac{3m_1}{4\pi\rho_1} + \frac{3m_2}{4\pi\rho_2}\right]^{1/3} \qquad (4)$$

where m_1 and m_2 are given by (1) and (2).

21. The specific weight of the inert carrier (Nonpareil 103) is ρ_0= 1580 g/L (density = 1.58). The layer containing the drug substance is deposited by spray coating, and its specific weight ρ_1 is assumed to be equal to 1200 g/liter (density = 1.2). Similarly, the specific weight of the coating ρ_2 is assumed to be equal to 1000 g/liter (density = 1). Spray coating processes

generally lead to porous layers with low apparent density. However, the porosity has been neglected in order to calculate the minimum size of the coated granules disclosed by Ishibashi.

22. Table 1, below, shows the calculated diameters of the coated granules for Ishibashi's Examples 1, 2, 3, 3bis, 4, 4bis, 5 and 5bis. As a result, the minimum diameter in microns can be 930 microns as shown in Example 1.

23. This number, however, is artificially small because Ishibashi does not state the concentration of sucrose solution used.

24. A typical sucrose solution used at this time would be at least about 60%.

25. I did not know the Ishibashi sucrose solution, so I did not use this into the calculations. Any sucrose solution would result in a larger diameter. Thus, by using sucrose, Ishibashi's Example 1 would have a diameter greater than 930 microns.

TABLE 1

N° of example	1	2	3	3bis	4	4bis	5	5bis
Neutral beads								
M0 (Kg)	0,05	0,05	0,05	0,05	0,05	0,05	0,05	0,05
ρ_0 (kg/m^3)	1580	1580	1580	1580	1580	1580	1580	1580
R_0 (m)	0,00023	0,00023	0,00023	0,00023	0,00023	0,00023	0,00023	0,00023
Drug-loaded core								
M1 (Kg)	0,23	0,33	0,23	0,23	0,23	0,23	0,23	0,23
ρ_1 (kg/m^3)	1200	1200	1200	1200	1200	1200	1200	1200
Coating								
%coating	30	67	30	40	120	140	50	60
M2 (Kg)	0,087	0,2546	0,084	0,112	0,336	0,392	0,14	0,168
ρ_2 (kg/m^3)	1000	1000	1000	1000	1000	1000	1000	1000
R2 (m)	0,00046646	0,00059987	0,00049077	0,00050524	0,00059918	0,00061854	0,00051892	0,00053192

N° of example	1	2	3	3bis	4	4bis	5	5bis
Diameter(micron)	930	1200	980	1010	1200	1230	1040	1060

26. Table 2, below, shows the same calculation made with the largest nonpareil 103 available at the time. This calculation shows that the particle size of Ishibashi coated granules could have been as high as 2430 to 3230 µm.

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TABLE 2

N° of example	1	2	3	3bis	4	4bis	5	5bis
Neutral beads								
M0 (Kg)	0,06	0,05	0,05	0,05	0,05	0,05	[illegible]	0,05
Π_0 (kg/m^3)	1580	1580	1580	1580	1580	1580	1580	1580
R_0 (m)	0,0006	0,0006	0,0006	0,0006	0,0006	[illegible]	[illegible]	0,0006
Drug-loaded core								
M1 (Kg)	0,23	0,33	0,23	0,23	0,23	0,23	0,23	0,23
Π_1 (kg/m^3)	1200	1200	1200	1200	1200	1200	1200	1200
Coating								
%coating	30	67	30	40	120	140	50	60
M2 (Kg)	0,087	0,2546	0,084	0,112	0,336	0,392	0,14	0,168
Π_2 (kg/m^3)	1000	1000	1000	1000	1000	1000	1000	1000
R2 (m)	0,00045646	0,00059987	0,00049077	0,00050524	0,00059918	0,00061854	0,00051892	0,00053192

N° of example	1	2	3	3bis	4	4bis	5	5bis
Diameter (micron)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

27. In conclusion, both Table 1 and Table 2 neglect the volume of sucrose, and hence underestimate the size of the coated granules disclosed in Ishibashi. It thus appears that the particle size of the coated granules is greater than 930 µm (if the smallest available nonpareil is used) or greater than 2430 µm (if the largest available nonpareil is used).

28. I declare that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.

Catherine CASTAN

dec. 18th 2009

Date

Appendix: Handbook of Pharmaceutical Excipients, 2nd Edition

A catalogue record for this book is available from the British Library.

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Sugar Spheres

1. Nonproprietary Names

USPNF: Sugar spheres

2. Synonyms

Non-pareil; *Non-pareil 103*; non-pareil seeds; *Nu-Core*; *Nu-Pareil*; sugar seeds.

3. Chemical Name and CAS Registry Number

—

4. Empirical Formula Molecular Weight

See Section 8.

5. Structural Formula

See Section 8.

6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Sugar spheres are used as inert cores in capsule and tablet formulations particularly multiparticulate sustained release formulations.[1,2] They form the base upon which a drug is coated, usually followed by a release modifying polymer coating. Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer, or due to the controlled erosion of the polymer coating. Complex drug mixtures contained within a single dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8. Description

The USPNF XVII describes sugar spheres as approximately spherical granules of a labelled nominal size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch. Usually white in color, sugar spheres may also contain approved coloring agents.

9. Pharmacopeial Specifications

Test	USPNF XVII
Identification (starch)	+
Specific rotation	+41° to +61°
Microbial limits	+
Loss on drying	≤ 4.0%
Residue on ignition	≤ 0.25%
Heavy metals	≤ 5 ppm
Particle size distribution	≤ 10% oversize, ≤ 10% undersize

10. Typical properties

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available (US standard sieves):

35-40 mesh (425-500 μm)
30-35 mesh (500-600 μm)
25-30 mesh (600-710 μm)
20-25 mesh (710-850 μm)
18-20 mesh (850-1000 μm)
16-20 mesh (850-1180 μm)
14-18 mesh (1000-1400 μm)

Solubility: solubility in water varies according to the sucrose to starch ratio. The sucrose component is freely soluble in water whereas the starch component is insoluble in cold water.

11. Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13. Method of Manufacture

Sugar spheres are prepared from crystalline sucrose which is coated using sugar syrup and a starch dusting powder

14. Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates and in higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the US.

17. Pharmacopeias

USPNF.

18. Related Substances

Compressible Sugar; Confectioner's Sugar; Starch; Sucrose.

19. Comments

—

20. Specific References

1. Narwathan R, Labhasetwar VD, Lakhota CL, Dorle A. Timed-release norcapine microcapsules. Indian J Pharm Sci 1988; 50: 120-122.
2. Bansal AK, Kakkar AP. Solvent deposition of diazepam over sucrose pellets. Indian J Pharm Sci 1990; 52: 186-187.

21. General References

Birch GG, Parker KJ, editors. Sugar: science and technology. London: Applied Science publications Ltd, 1979.

22. Authors

UK: RC Moreton.

Appendix 2: Handbook of Pharmaceutical Excipients, 3rd edition

Published by the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA
www.aphanet.org
and the Pharmaceutical Press
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www.pharmpress.com

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Loss on drying	≤ 4.0%
Residue on ignition	≤ 0.25%
Heavy metals	≤ 5 ppm
Particle size distribution	+
Organic volatile impurities	+
Sucrose (dried basis)	62.5-91.5%

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